TWELFTH ANNUAL REPORT 2003

CREUTZFELDT-JAKOB DISEASE SURVEILLANCE IN THE UK

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SUMMARY

The national surveillance programme for Creutzfeldt-Jakob disease (CJD) in the UK was initiated in May 1990. In 1999, the National CJD Surveillance Unit (NCJDSU) became a WHO Collaborative Centre for Reference and Research on the surveillance and epidemiology of human transmissible encephalopathies (TSEs). In September 2001 the National Care Team was formed, which since March 2003 comprises 2 care coordinators and a secretary. The National Care Team is based within the NCJDSU and was formed in response to concerns regarding the care of CJD patients.

The information provided in this twelfth report continues to provide evidence of a high level of case ascertainment. Detailed clinical and epidemiological information has been obtained for the great majority of patients. The methodology of the case-control study for risk factors of CJD has been altered in an attempt to overcome some logistic problems in its conduct. The post mortem rate for patients with suspected CJD is high, although there is ongoing evidence that this rate continues to decline, in line with general autopsy rates in the UK. This is reflected in the reduced number of brain specimens examined in the neuropathology laboratory this year, particularly for variant CJD.

In 1990-2003 mortality rates from sporadic CJD in England, Scotland, Wales and Northern Ireland were, respectively, 0.86, 0.84, 1.08 and 0.57/million/year. The difference between the rates in each country is not statistically significant ($p>0.2$). These rates are comparable to those observed in other countries in Europe and elsewhere in the world, including countries which are free of BSE. There was some variation in the observed mortality rates between the different regions within the UK but this variation is not statistically significant ($p>0.2$). The highest and lowest mortality rates from sporadic CJD were observed in the South West (SMR=129) and Northern Ireland (SMR=79).

Up to 31 December 2003, there have been 139 deaths from definite or probable variant CJD (vCJD) in the UK. Of these, 104 were confirmed by neuropathology. The clinical, neuropathological and epidemiological features of these cases of vCJD are remarkably uniform and consistent with our previous descriptions. Analysis of the incidence of vCJD onsets and deaths from January 1994 to December 2003 shows evidence that the epidemic may have reached a peak or a plateau. While this is an encouraging finding, incidence of vCJD may increase again, particularly if different genetic subgroups are found to be affected.

Risk factors for the development of vCJD include age, residence in the UK and methionine homozygosity at codon 129 of the prion protein gene - 123 cases of vCJD with available genetic analysis have all been methionine homozygotes. The incidence of vCJD across the UK continues to show a "North-South" difference (though slightly less than previously reported), with a higher incidence being maintained in the North of the UK. The underlying reason for this finding is not clear. The only statistically significant geographic cluster of vCJD cases in the UK was in Leicestershire. All geographically associated cases of vCJD are considered for investigation according to a protocol which involves the NCJDSU, colleagues at the HPA, SCIEH and local public health physicians.

The activities of the NCJDSU are strengthened by collaboration in other surveillance projects, including the Transfusion Medicine Epidemiology Review and the study of Progressive Intellectual and Neurological Deterioration in Children. The collaboration of our colleagues in these projects is greatly appreciated; the effectiveness of this collaboration allowed the identification in 2003 of a case of variant CJD associated with blood transfusion. The success of the National CJD Surveillance Project continues to depend on the extraordinary level of co-operation from the neuroscience community and other medical and paramedical staff throughout the UK. We are particularly grateful to the relatives of patients for their help with this study.

Section

2

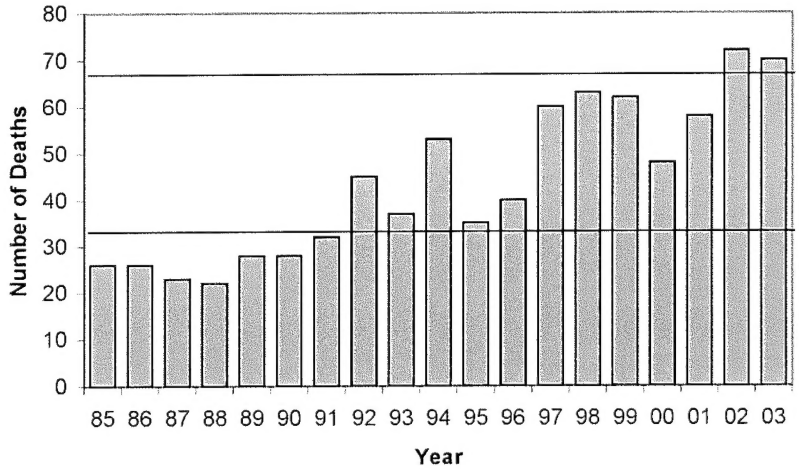
CLINICAL SURVEILLANCE

The national surveillance of CJD in the UK was initiated in May 1990 in response to a recommendation in the Report of the Working Party on Bovine Spongiform Encephalopathy (Southwood Committee). The surveillance is funded by the Department of Health and by the Scottish Executive Health Department. The initial aim of the NCJDSU was to identify any change in the pattern of CJD that might be attributable to human infection with the agent responsible for the emergence of bovine spongiform encephalopathy (BSE) in cattle. Such a change was recognised in 1996 when vCJD was first described. The NCJDSU now aims to monitor characteristics of CJD, specifically sporadic CJD and variant CJD, to identify trends in incidence rates and to study risk factors for the development of disease. This report documents the findings in relation to UK cases of sporadic, familial, iatrogenic and variant CJD referred up to 31st December 2003 (with data ascertained up to 14th April 2004). Data from England and Wales include retrospective data from 1970; for Scotland and Northern Ireland, retrospective data are available from 1985.

2.1 Sporadic Creutzfeldt-Jakob Disease

Between 1st January 1970 and 31st December 2003, 1107 cases of sporadic CJD were identified in the UK, of which 11 cases were still alive on 31st December 2003. Two further cases were identified in Jersey but they were not included in the following UK analyses. Of these UK cases, 848 (77%) were classified as definite cases with the remainder classed as probable. Figure 1a shows the number of deaths each year from sporadic CJD for the UK between 1985 and 2003, Figure 1b shows similar data for England and Wales between 1970 and 2003 and Figure 1c shows the number of deaths from sporadic CJD in Scotland and Northern Ireland between 1985 and 2003. In England and Wales the number of deaths identified each year increased from an average of about 10 per year at the beginning of the 1970s, to about 40 per year in the 1990s. A similar phenomenon has been observed in other European countries and this probably largely reflects improved case ascertainment. Over the shorter time period for which data are available for Scotland and Northern Ireland there is no clear secular trend. Over the period 1990-2003 the average crude annual mortality rates from sporadic CJD per million population were 0.86 in England, 1.08 in Wales, 0.84 in Scotland and 0.57 in Northern Ireland, as shown in Table 1. When account is taken of age and sex, the variation in recorded mortality between the different countries is not statistically significant ($p > 0.2$).

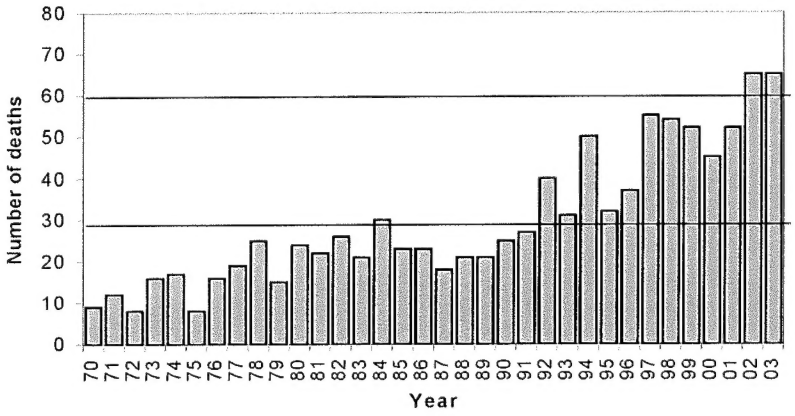
Figure 1a **Deaths from sporadic CJD, UK, 1985-2003**



Note: The horizontal lines indicate the number of deaths approximately equivalent to crude mortality rates of 0.5 and 1 per million per year

Data for 2003 may be incomplete

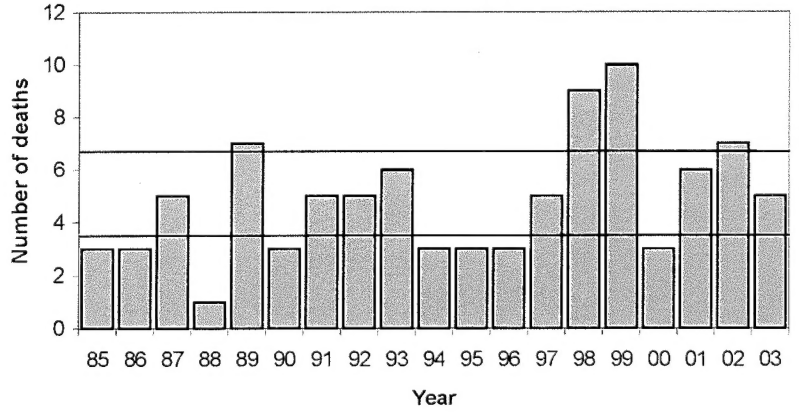
Figure 1b **Deaths from sporadic CJD, England and Wales, 1970-2003**



Note: The horizontal lines indicate the number of deaths approximately equivalent to crude mortality rates of 0.5 and 1 per million per year

Data for 2003 may be incomplete

Figure 1c **Deaths from sporadic CJD, Scotland and Northern Ireland 1985-2003 (please note different scale from Figs 1a and 1b)**



Note: The horizontal lines indicate the number of deaths approximately equivalent to crude mortality rates of 0.5 and 1 per million per year

Data for 2003 may be incomplete

Table 1 Deaths from definite and probable sporadic CJD by region and county of death: 1 January 1990 to 31st December 2003

	No of cases	Total no (mortality rate/million/ annum)*
ENGLAND		
North		
Cleveland	4	
Cumbria	9	
Durham	6	36 (0.83)
Northumberland	3	
Tyne & Wear	14	
East Midlands		
Derbyshire	9	
Leicestershire	13	
Lincolnshire	7	43 (0.75)
Northamptonshire	2	
Nottinghamshire	12	
South East		
Bedfordshire	5	
Berkshire	10	
Buckinghamshire	5	
East Sussex	10	
Essex	26	
Greater London	62	203 (0.81)
Hampshire	22	
Hertfordshire	10	
Isle of Wight	2	
Kent	17	
Oxfordshire	9	
Surrey	10	
West Sussex	15	
North West		
Cheshire	12	
Greater Manchester	25	77 (0.86)
Lancashire	20	
Merseyside	20	
WALES		
Clwyd	6	
Dyfed	4	
Gwent	6	
Gwynedd	9	
Mid Glamorgan	10	
Powys	2	
South Glamorgan	3	
West Glamorgan	4	
TOTAL FOR WALES		**44 (1.08)**
NORTHERN IRELAND	13	**13 (0.57)**

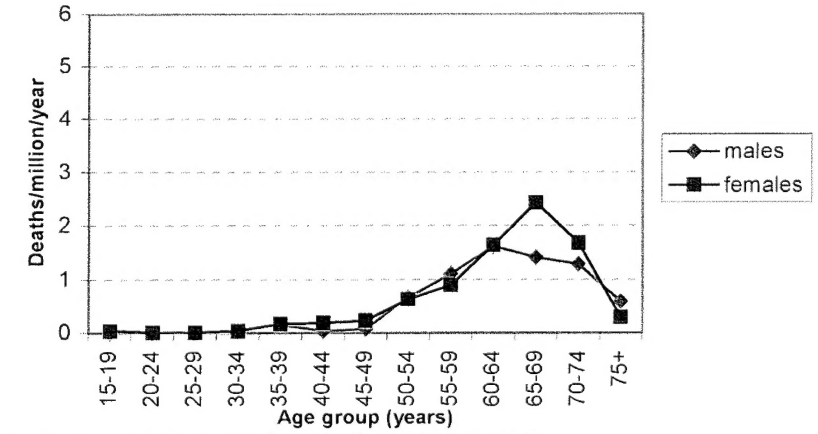
	No of cases	Total no (mortality rate/million/ annum)*
ENGLAND		
Yorkshire & Humberside		
Humberside	8	
NorthYorkshire	13	
South Yorkshire	19	61 (0.87)
West Yorkshire	21	
East Anglia		
Cambridgeshire	6	
Norfolk	12	30 (1.02)
Suffolk	12	
South West		
Avon	15	
Cornwall	10	
Devon	14	
Dorset	17	82 (1.22)
Gloucestershire	9	
Somerset	8	
Wiltshire	9	
West Midlands		
Hereford & Worcs.	5	
Shropshire	4	
Staffordshire	15	53 (0.71)
Warwickshire	2	
West Mids (Met)	27	
TOTAL FOR ENGLAND		**586†(0.86)**
SCOTLAND		
Borders	2	
Central	5	
Dumfries & Galloway	0	
Fife	2	
Grampian	8	
Highland	1	
Lothian	16	
Strathclyde	22	
Tayside	2	
Islands (Shetland)	2	
Islands (Orkney)	0	
Islands (Western Isles)	0	
TOTAL FOR SCOTLAND		**60 (0.84)**

† includes one case where address is unknown

* based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the 14-year period of the study.

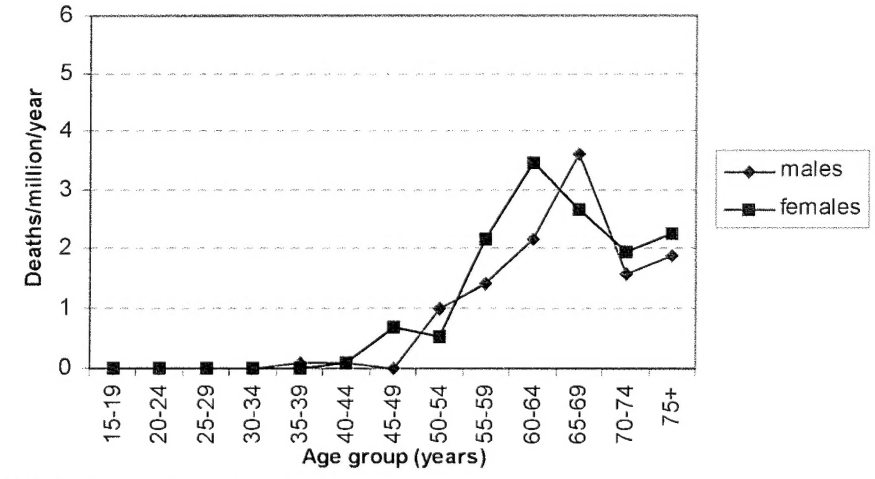
Figure 2a, 2b and 2c shows average annual age- and sex-specific mortality rates over the time periods 1970-89, 1990-95 and 1996-03, respectively. The median ages of cases at death during these time periods were 64, 66 and 67 years, respectively. In all three time periods, the mortality rates below 40 years of age were extremely low (< 0.2/million/year). Thereafter, in all three periods, the mortality rates increased until the ages of 60-74 years and then declined. The decline in mortality rate in the older age groups was more marked prior to 1990. The mortality rate in those aged 75 years and above was 2.78 cases/million/year in 1996-03, 2.11 cases/million/year in 1990-95 and 0.38 cases/million/year in 1970-89. This might be explained by an increase in case ascertainment in the elderly over time. Another feature over the time period studied, a change in the sex ratio, affecting particularly older cases, with a male excess after 1996, was examined in the 2001 annual report. The explanation for this trend remains unclear.

Figure 2a Age- and sex-specific mortality rates from sporadic CJD in the UK 1970-1989
(note: from 1970-1984 only England & Wales, thereafter UK)



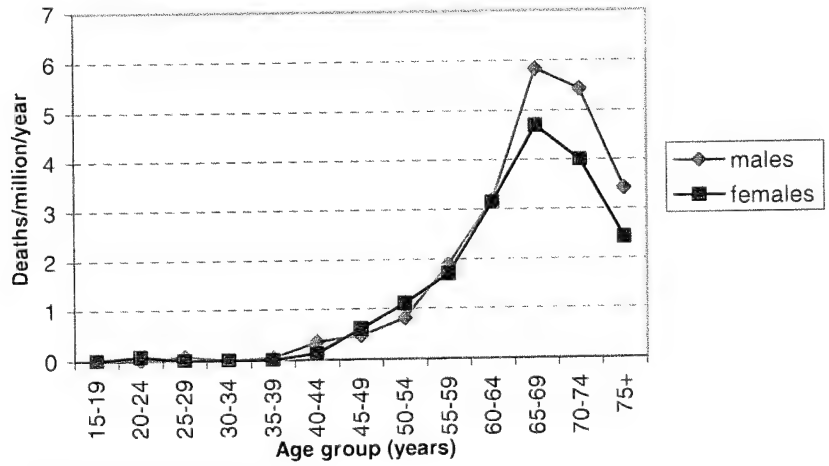
Mortality rates calculated using 1981 Census for GB and 1991 Census for NI

Figure 2b Age- and sex-specific mortality rates from sporadic CJD in the UK 1990-1995



Mortality rates calculated using 1991 Census

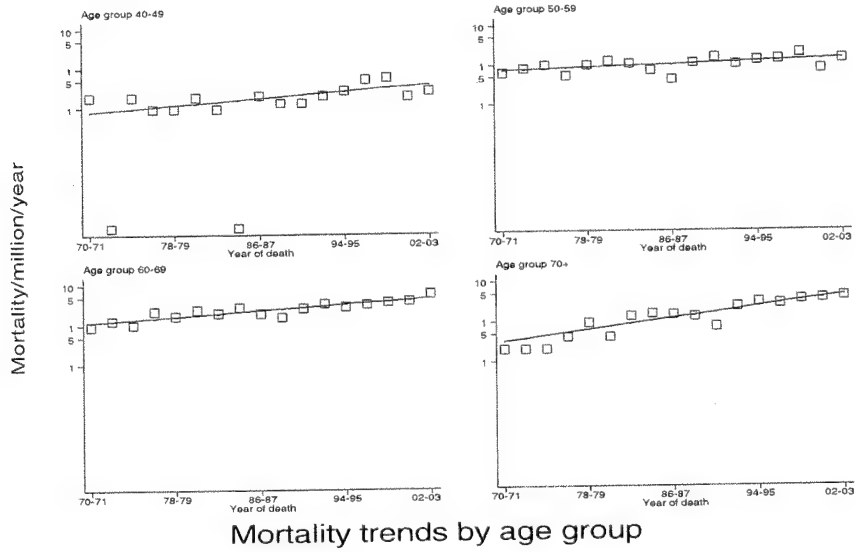
Figure 2c Age- and sex-specific mortality rates from sporadic CJD in the UK 1996-2003



Mortality rates calculated using 2001 Census

An analysis of age specific trends from 1970 to 2003 (Figure 3) shows there has been an increase in recorded mortality over time in all age groups, but that the greatest relative increase has occurred in those aged 70 years and above. Currently the mortality rate in this age group is similar to that in the age group 60-69 years. The temporal increases in mortality are statistically significant in all age groups ($p=0.004$, $p=0.003$, $p<0.001$, $p<0.001$ for age groups 40-49, 50-59, 60-69 and ≥70 years respectively). These observations are consistent with improved case ascertainment in all ages, but with the greatest increase occurring in the elderly.

Figure 3 Trends in mortality from sporadic CJD by age: 1970-2003



Mortality rates calculated using 1981, 1991 & 2001 Census for time periods 1970-1985, 1986-1995 and 1996-2003 respectively.

Table 2 presents, by 2-year period, the numbers of deaths underlying these trends. These data emphasise the very small numbers of cases of sporadic CJD occurring in individuals aged <50 years. They show clearly the substantial increase in the numbers of deaths identified among those aged 70 years and above, from around one per year in England and Wales in the early 1970s to around 25 per year in the UK in recent years.

Table 2 **Cases of sporadic CJD in England and Wales (from 1970) and the UK (from 1985) by two year period**

Age at death (yrs)	Year of death																	
	70-71	72-73	74-75	76-77	78-79	80-81	82-83	84-85[1]	86-87	88-89	90-91	92-93	94-95	96-97	98-99	00-01	02-03[2]	Total[2]
10-19	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	**1 (0)**
20-29	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	**2 (0)**
30-39	1	0	0	2	2	1	1	4	1	0	1	0	0	0	1	0	0	**14 (0)**
40-49	2	0	2	1	1	2	1	0	3	2	2	3	4	8	9	3	4 (1)	**47 (1)**
50-59	7	9	11	6	11	14	12	8	5	13	18	12	15	20	28	11	20 (5)	**220 (5)**
60-69	9	13	10	22	17	24	20	28	22	18	30	39	32	35	40	43	64 (4)	**466 (4)**
70-79	2	2	2	4	9	4	11	16	18	14	7	21	34	30	35	38	46 (1)	**293 (1)**
80-89	0	0	0	0	0	0	2	0	0	2	2	7	3	6	10	11	7	**50 (0)**
90+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	**2 (0)**
Total	**21**	**24**	**25**	**35**	**40**	**46**	**47**	**56**	**49**	**50[3]**	**60**	**82**	**88**	**100**	**125**	**106**	**142 (11)**	**1096[3] (11)**

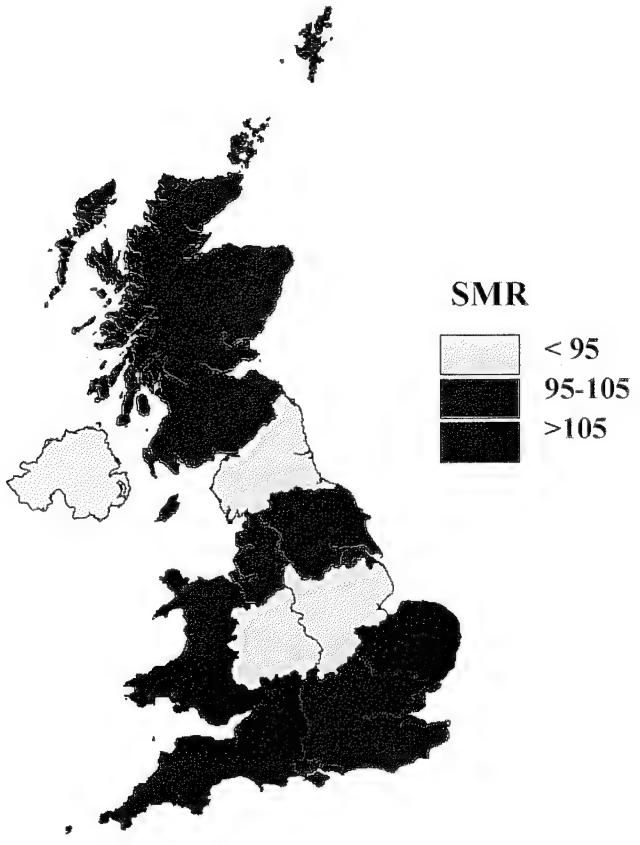
[1] Up to 1984, cases from England and Wales only. From 1985 onwards, cases from Scotland and Northern Ireland are included

[2] Deaths up to 31st December 2003. Numbers in parentheses indicate additional cases alive on 31st December 2003. Data for 2003 not yet complete.

[3] Total includes one case whose age at death was unknown

Age- and sex- standardised mortality ratios (SMRs) for the 11 standard regions of the UK for the period 1st January 1990 to 31st December 2003 were calculated (Figure 4). After adjusting for the age/sex distribution of the population, the variation in mortality rates between the different regions is not statistically significant ($p>0.2$). Regions of relatively high mortality are South West (SMR=129), Wales (SMR=117) and East Anglia (SMR=114). Low mortality rates were observed in Northern Ireland (SMR=79), West Midlands (SMR=83) and East Midlands (SMR=87). The SMRs for the other five regions all lay between 93 and 100. The highest SMR (129 in South West) arose from 82 cases observed compared with 64 expected, an excess of about 1.4 cases every year compared to the national average. In Wales and East Anglia the total numbers of excess cases were approximately 6 and 4 respectively.

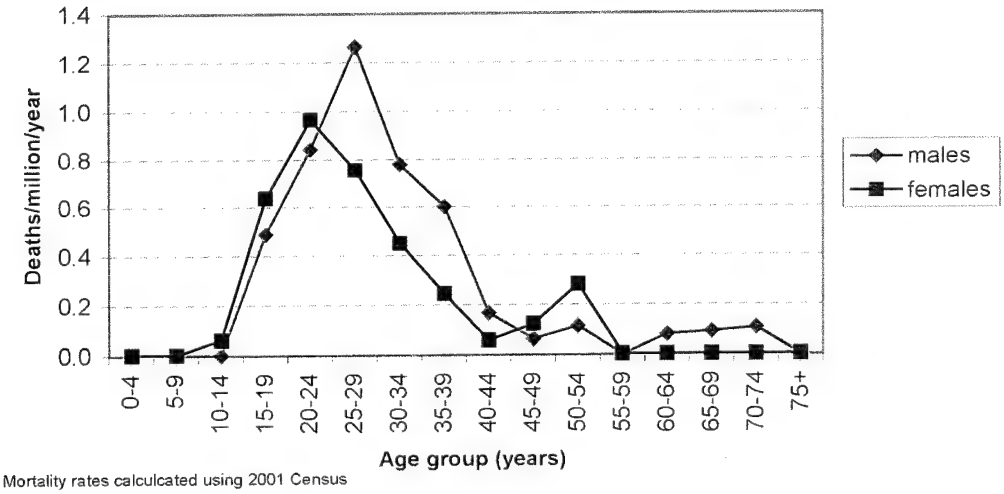
Figure 4 Standardised mortality ratios (SMRs) by standard region, UK 1 January 1990 - 31 December 2003



2.2 Variant Creutzfeldt-Jakob Disease

Up to 31st December 2003, 145 cases of definite or probable vCJD had been identified in the UK (104 definite, 35 probable who did not undergo post mortem and 6 probable cases still alive). Sixty-three (43%) of the 145 cases were women. The median age at onset of disease was 26 years and the median age at death 28 years (compared with 66 years for the median age at onset and 67 years for the median age at death for sporadic CJD). The youngest case was aged 12 years at onset while the oldest case was aged 74 years. The age- and sex-specific mortality rates for vCJD over the time period 1 May 1995 to 31 December 2003 are shown in Figure 5. The median duration of illness from the onset of first symptoms to death was 14 months (range 6-39). The median duration of illness for cases of sporadic CJD was 4 months (range 1 to 74) during the period 1990-2003.

Figure 5 **Age- and sex-specific mortality rates from vCJD in the UK 1 May 1995 - 31st December 2003**



Mortality rates calculcated using 2001 Census

Incidence of vCJD onsets and deaths from January 1994 - December 2003

Each quarter data on diagnosed cases of variant Creutzfeldt-Jakob disease (vCJD) in the UK are reviewed in order to investigate trends in the underlying rate at which disease onsets and deaths are occurring. The following analysis reviews the data to the end of December 2003 by which time there was a total of 145 cases of which 139 had died.

Methods

Onsets:

The incidence of onsets by quarter was analysed with Poisson models using polynomials (constant, exponential, quadratic exponential). When modelling the incidence of onsets over time, delay to diagnosis, and the fact that this delay may be shortening over time because of new diagnostic methods, must be taken into account. Consequently the data were cross-classified by quarter of onset and number of quarters delay from onset to diagnosis, and the delay from onset to diagnosis modelled using a gamma distribution with a mean that can vary over time.

Deaths:

After grouping deaths by quarter the incidence of deaths were modelled by Poisson regression using polynomials. Most deaths are reported quickly so an adjustment for reporting delay is not necessary. So far the age at death has not increased as might have been expected, assuming that most exposure to BSE ceased in the early 1990s. In order to examine this further the cases were stratified by quarter of death and birth cohort (pre1970, 1970s and 1980s). Trends in deaths over time were compared between these cohorts.

Also, to investigate further whether the epidemic has reached a peak an alternative model was considered using annual data in which incidence rises to a plateau and then remains constant.

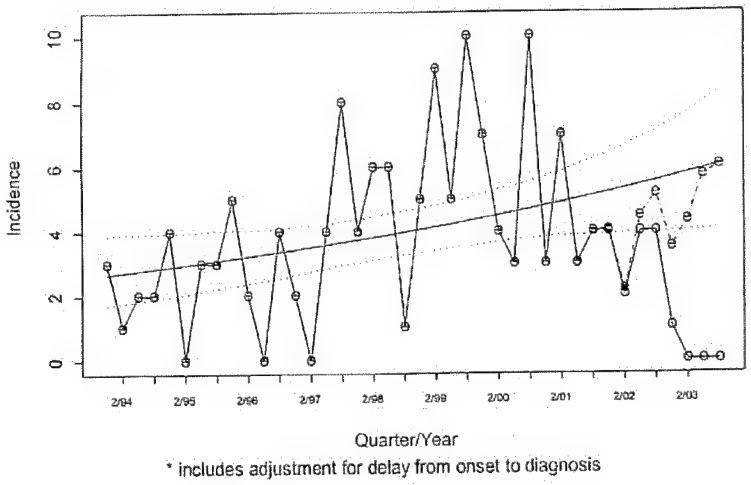
Results for Onsets

Since vCJD was first identified, the average interval between the onset of first symptoms and the diagnosis of vCJD has decreased. The mean delay to diagnosis is estimated to have reduced by an average of 5% per year and is currently estimated at 10 months.

Figure 6a shows the observed and expected number of onsets and the estimated trend (assuming exponential growth) with 95% confidence intervals (CIs). This model estimates that the number of onsets have increased by 9% per year since 1994 (95%CI 1.3-16). The estimated incidence in the current quarter is 6.1 cases per quarter.

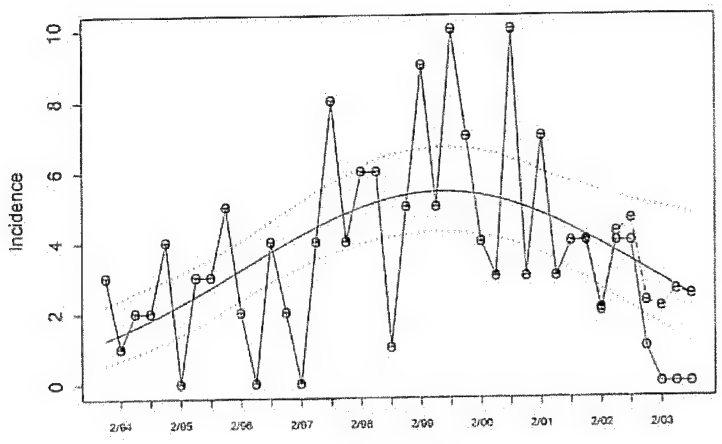
A separate model including a quadratic trend showed evidence of a better fit (p=0.001 for quadratic term). Figure 6b shows the quadratic model fitted to the data. The quadratic model is consistent with an epidemic that has reached a peak and this model gives an estimated current incidence of 2.5 onsets per quarter. If the quadratic model is assumed to be correct then the peak is estimated to have occurred in September 1999 with a 95% CI for the time of the peak from December 1998 to June 2001.

Figure 6a: Observed (-o-) and expected (-e-) quarterly incidence of vCJD onsets Fitted exponential trend* (__) is given with its 95% confidence limits (...)



* includes adjustment for delay from onset to diagnosis

Figure 6b: Observed (-o-) and expected (-e-) quarterly incidence of vCJD onsets Fitted quadratic trend* (__) is given with its 95% confidence limits (...)



Predicted onsets by the end of December 2003

Based upon the exponential model, the estimated total number of cases with onset by December 2003 is 165 (145 already diagnosed +20 not yet diagnosed) with a 95% prediction interval of 158 to 174. Based on the quadratic model, however, the estimated total number of cases with onset by December 2003 is 155 (145 already diagnosed + 10 not yet diagnosed) with a 95% prediction interval of 150 to 162.

Results for Deaths

All deaths combined

Figure 7a shows the observed numbers of deaths by quarter with the exponential model fitted. The annual number of deaths has increased by an estimated 13% per year, (95% CI, 5-20). Based on this model the estimate of the current quarterly incidence of deaths is 6.2.

The model that included a quadratic term provides a better fit to the data (p=0.0003) indicating strong evidence of a departure from a constant exponential increase. Figure 7b shows the data with the fitted quadratic trend. This model estimates that the current quarterly incidence of deaths is 3.5. If the quadratic model is assumed to be correct then the peak is estimated to have occurred in December 2000 with a 95% CI for the time of the peak from March 2000 to August 2002.

An alternative model in which the incidence of deaths rises to a plateau was also fitted to the annual data (Figure 7c). This model, which gave an estimate for the plateau at 19.5 deaths per year (4.9 per quarter), fitted the observed incidence of deaths as well as the quadratic model with neither model showing evidence of lack of fit. Therefore it is not possible to distinguish between a trend that has reached a peak and one that has reached a plateau.

Figure 7a Observed (-o-) quarterly incidence of vCJD deaths
Fitted underlying trend (__) is given with its 95% confidence limits (...)

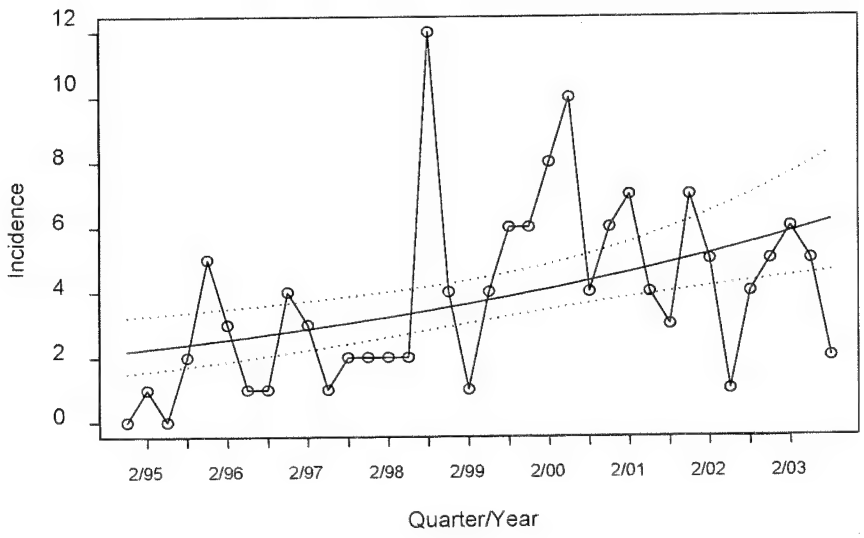


Figure 7b Observed (-o-) quarterly incidence of vCJD deaths
Fitted underlying quadratic trend (__) is given with its 95% confidence limits (...)

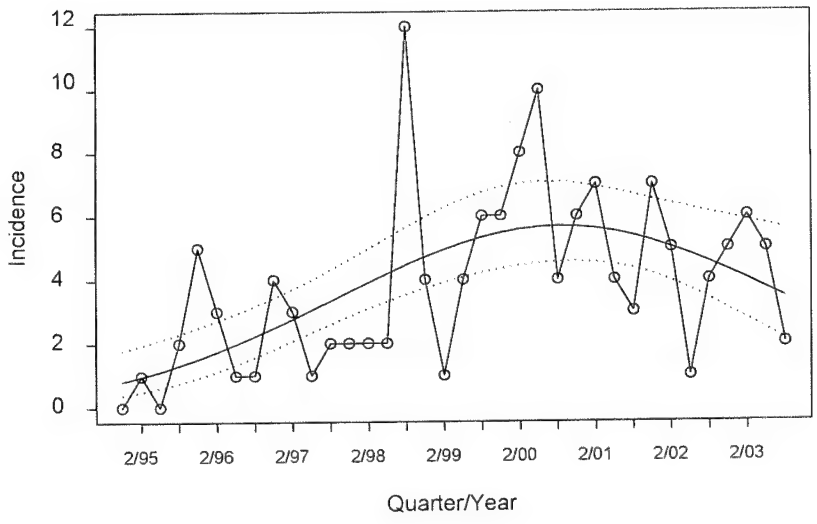
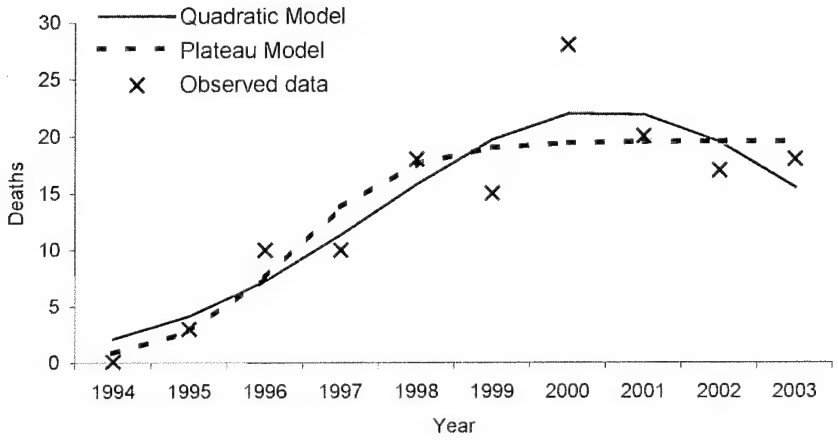


Figure 7c Quadratic-exponential and plateau models for vCJD deaths incidence trend



Predictions for deaths in 2004

From the model with an increasing exponential trend, the predicted total number of deaths for 2004 is 27 with a 95% prediction interval of 16 to 39. However the model with the quadratic term predicts a total of 11 deaths for 2004 with a 95% prediction interval of 4 to 19. The plateau model predicts a total of 19 deaths for 2004 with a 95% prediction interval of 10 to 29.

Assessment of Predictions made at the end of December 2002

The exponential model predicted 28 deaths for 2003 with a 95% prediction interval of 16-40, whereas the quadratic model predicted 13 deaths with a 95% prediction interval of 5-23. The observed number of deaths was 18. Although this is within both prediction intervals it is closer to the prediction by the quadratic model.

Deaths by cohort

The age at death has so far remained stable, contrary to what might be expected given that most exposure to BSE is presumed to have ceased in the early 1990s. This finding is consistent with, for example, varying age-specific susceptibility or exposure or possibly different incubation periods by age. To examine this in more detail the epidemic curves (quadratic model) are compared in those born before 1970 with those born in the 1970s and the 1980s. This analysis revealed evidence of differences between cohorts in the shape of the fitted curves ($p<0.001$). The main difference is that in the 1980s cohort no deaths were seen prior to 1999. Figure 8 shows the fitted quadratic epidemic curves for each of the cohorts. The data are compatible with the shapes of the curves in the pre 1970s cohort and the 1970s cohort being the same ($p=0.15$). Note that in the 1980s cohort the confidence intervals are very wide due to small numbers and it is unclear in this cohort whether or not the trend is still exponential.

Figure 8a Quarterly incidence of vCJD deaths (born pre 1970 cohort)
Fitted underlying quadratic trend is given with its 95% confidence limits

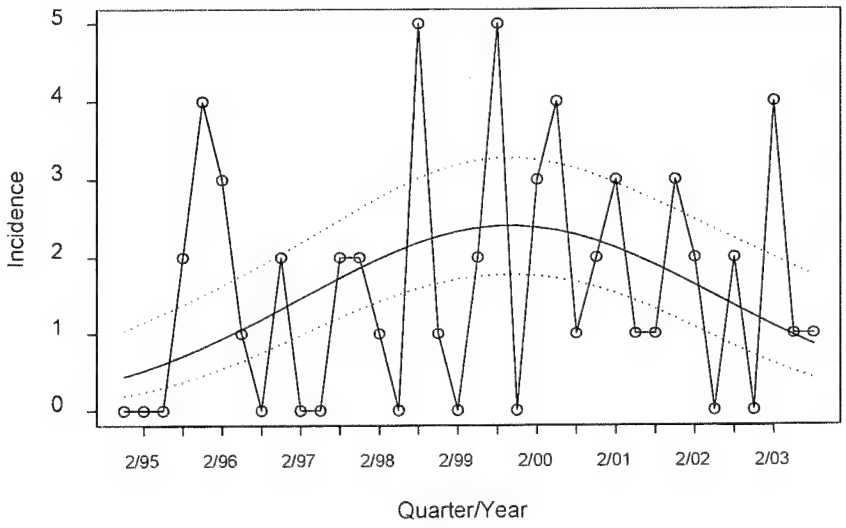


Figure 8b Quarterly incidence of vCJD deaths (born 1970s cohort)
Fitted underlying quadratic trend is given with its 95% confidence limits

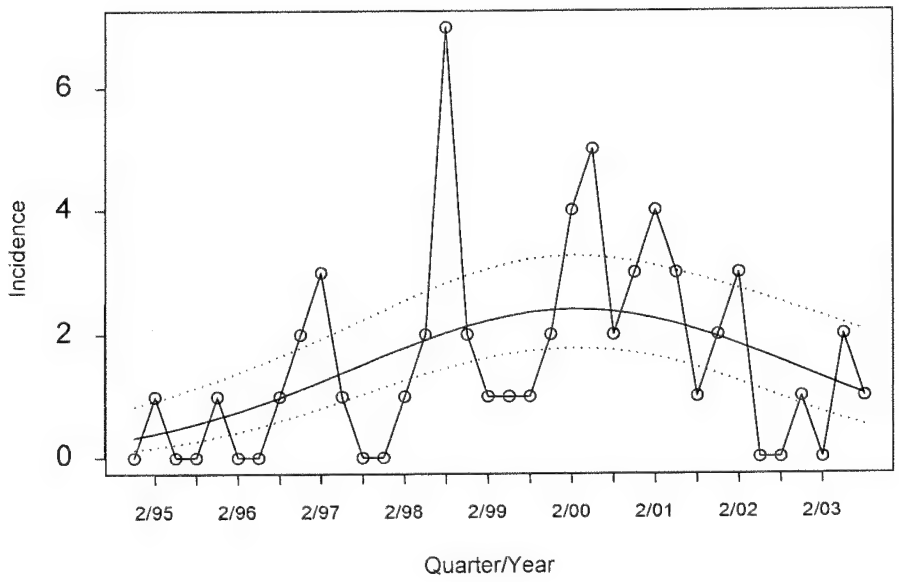
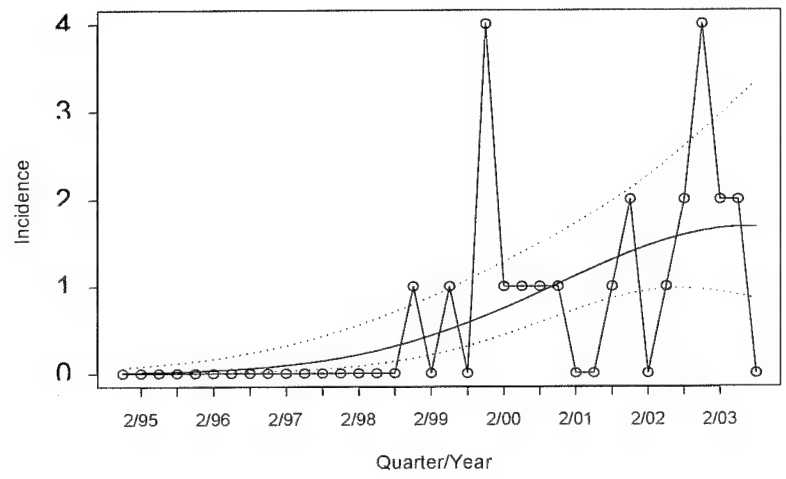


Figure 8c **Quarterly incidence of vCJD deaths (born 1980s cohort)**
Fitted underlying quadratic trend is given with its 95% confidence limits



Summary

There is statistically significant evidence (p=0.001 for death, p=0.0003 for disease onset) that the epidemic is no longer increasing exponentially. Furthermore estimates from quadratic models fitted to the incidence suggest that the epidemic may have reached a peak. Estimates for the time of this peak are September 1999 (95% CI: December 1998-June 2001) for disease onset and December 2000 (95% CI: March 2000-August 2002) for deaths. Although these models suggest a peak may have been reached, analysis of the annual number of deaths indicates that an alternative model with an increase to a plateau of 19 deaths per year rather than a peak is also consistent with the data. That the epidemic may have reached and passed one peak does not exclude the possibility of further peaks in the future.

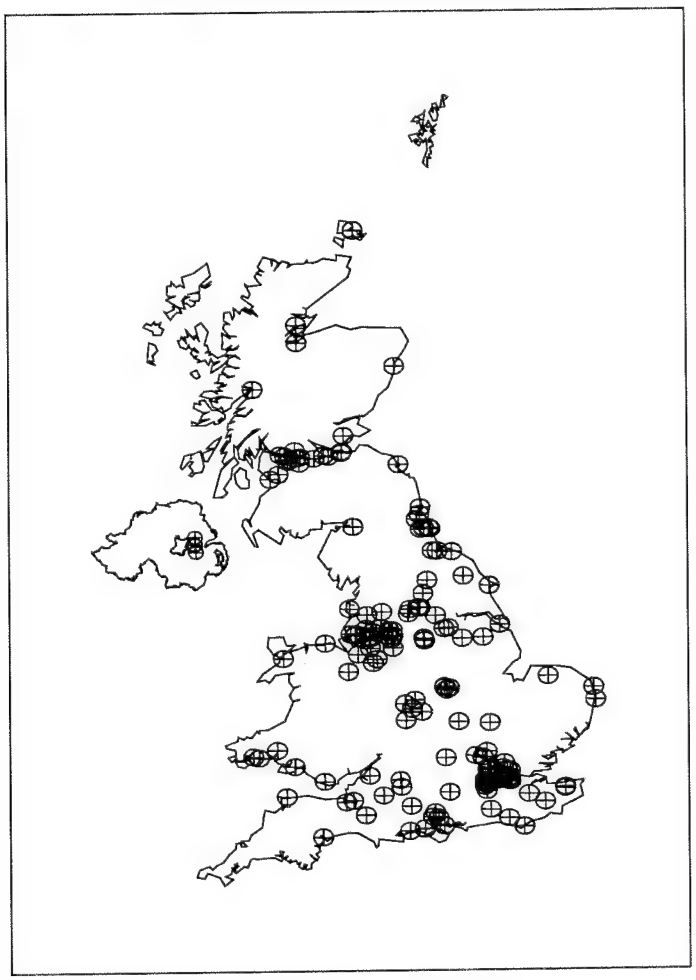
For the purposes of short-term predictions the model used is important; predictions are best made based on the quadratic model or plateau model rather than the exponential model which has a poor fit. The quadratic models estimate the current incidence of onsets to be 2.5 per quarter and deaths to be 3.5 per quarter with 11 deaths predicted for 2004 (95% prediction interval 4 to 19). The plateau model estimates the current incidence of deaths to be 4.9 per quarter with 19 deaths for 2004 (95% prediction interval 10 to 29). A plateau model has not as yet been fitted to the onsets data.

An analysis of deaths by birth cohort (pre 1970, 1970s, 1980s) indicates that the shape of the epidemic differs between cohorts, mainly due to the fact that deaths of individuals born in the 1980s only occurred from 1999 onwards.

Geographical distribution of variant CJD

Figure 9 shows the geographical distribution, by place of residence at onset, of 143 cases of vCJD in the UK for whom a residential address at onset is available. For one case the address at onset is known only at county level and for a further case residential address at onset is not known. Cases have been widely spread throughout the UK. Table 3 presents data on the geographical distribution, by county of residence at onset, of the cases who had died by 31st December 2003 (for whom information on place of residence at onset was available) along with the crude mortality rate per million population per annum of each standard region.

Figure 9 Geographical distribution of places of residence at onset of symptoms of vCJD (n=143*)



* in one case only county of residence was known and could not be plotted and in one case address at onset was not known and could not be plotted.

Table 3 Deaths from definite and probable vCJD by region and county of onset: 1 May 1995 to 31st December 2003 (n=138†)

	No of cases	Total no (mortality rate/million/ annum)*
ENGLAND		
North		
Cleveland	3	
Cumbria	1	
Durham	1	11 (0.41)
Northumberland	2	
Tyne & Wear	4	
East Midlands		
Derbyshire	0	
Leicestershire	4	
Lincolnshire	2	7 (0.20)
Northamptonshire	1	
Nottinghamshire	0	
South East		
Bedfordshire	0	
Berkshire	0	
Buckinghamshire	0	
East Sussex	2	
Essex	0	
Greater London	15	37 (0.24)
Hampshire	6	
Hertfordshire	3	
Isle of Wight	0	
Kent	4	
Oxfordshire	1	
Surrey	5	
West Sussex	1	
North West		
Cheshire	7	
Greater Manchester	7	20 (0.36)
Lancashire	3	
Merseyside	3	
WALES		
Clwyd	1	
Dyfed	3	
Gwent	0	
Gwynedd	1	
Mid Glamorgan	0	
Powys	0	
South Glamorgan	1	
West Glamorgan	1	
TOTAL FOR WALES		**7 (0.28)**
NORTHERN IRELAND	2	**2 (0.14)**

	No of cases	Total no (mortality rate/million/ annum)*
ENGLAND		
Yorkshire & Humberside		
Humberside	2	
NorthYorkshire	2	
South Yorkshire	4	13 (0.30)
West Yorkshire	5	
East Anglia		
Cambridgeshire	1	
Norfolk	2	4 (0.22)
Suffolk	1	
South West		
Avon	0	
Cornwall	1	
Devon	2	
Dorset	1	10 (0.24)
Gloucestershire	0	
Somerset	4	
Wiltshire	2	
West Midlands		
Hereford & Worcs.	0	
Shropshire	1	
Staffordshire	0	6 (0.13)
Warwickshire	1	
West Mids (Met)	4	
TOTAL FOR ENGLAND		**108 (0.26)**
SCOTLAND		
Borders	0	
Central	0	
Dumfries & Galloway	0	
Fife	1	
Grampian	1	
Highland	3	
Lothian	4	
Strathclyde	11	
Tayside	0	
Islands (Shetland)	0	
Islands (Orkney)	1	
Islands (Western Isles)	0	
TOTAL FOR SCOTLAND		**21 (0.47)**

* based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the 8.67 year period of the study.

† does not include 6 cases still alive at 31st December 2003 plus one case where address at onset was not known.

Table 4 shows cumulative regional rates of vCJD based on cases' place of residence in 1991, rather than at onset, and the population aged 10 years and above resident at that time. We originally performed an analysis of the first 51 cases, distinguishing two areas. The "North" comprised four standard regions: Scotland, North, Yorkshire and Humberside, North West. The "South" comprised the remaining 6 regions: Wales, West Midlands, East Midlands, East Anglia, South West, South East.

Age- and sex- standardised "incidence" ratios (SIRs) based on cases' place of residence in 1991 are shown in Figure 10 for the 11 standard regions of the UK.

Table 4 Distribution of 143* vCJD cases by standard region of residence on 1st January 1991

Standard region (in order of latitude of the centre of the region)	Population aged 10 years and above at the 1991 census	Number (cumulative incidence/million) of vCJD cases by place of residence in 1991
Scotland	4,363,684	17 (3.90)
North	2,635,785	11 (4.17)
Yorkshire & Humberside	4,202,051	14 (3.33)
North-West	5,396,333	22 (4.08)
East Midlands	3,444,391	11 (3.19)
West Midlands	4,464,592	8 (1.79)
East Anglia	1,775,687	4 (2.25)
Wales	2,466,669	5 (2.03)
South-East	15,010,650	37 (2.46)
South-West	4,055,268	11 (2.71)
Northern Ireland	1,320,430	3 (2.27)
Total	49,135,540	143 (2.91)

*Place of residence in 1991 not known for 2 cases.

Figure 10 **Standardised incidence ratios (SIRs) up to 31st December 2003 of vCJD by standard region on 1st January 1991**

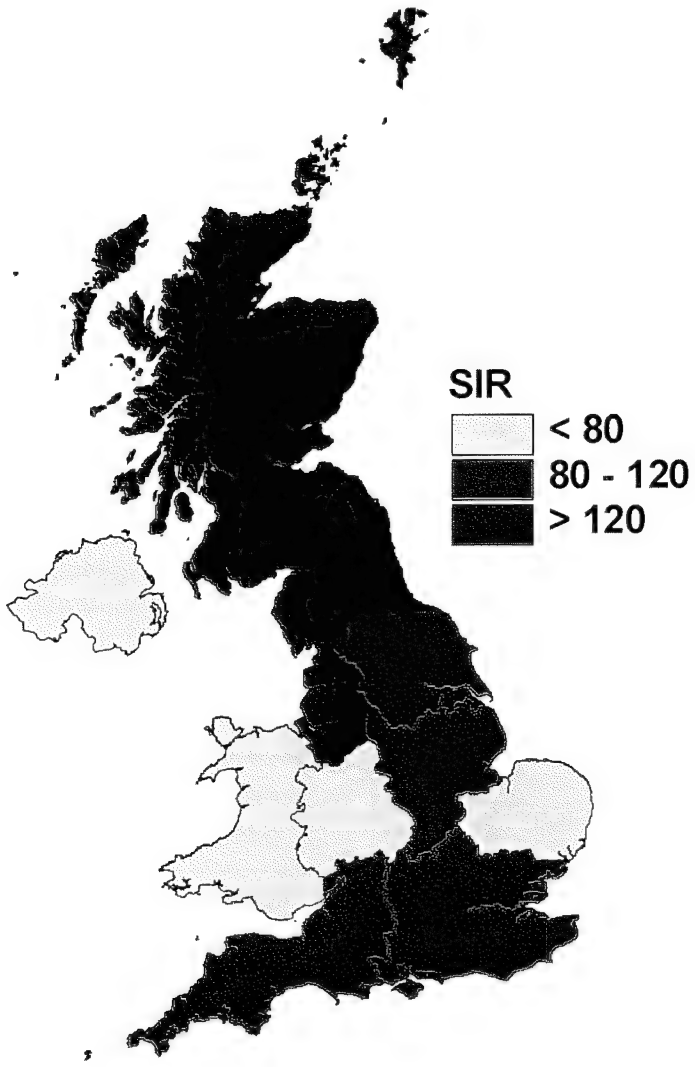


Table 5 shows the distribution of cases between the "North" and the "South" according to place of residence in 1991, for those cases included in the initial analysis (51) and for all cases. The excess of cases previously identified in the "North" (rate ratio controlling for age and sex = 1.94; 95% c.i. 1.12, 3.36) has been largely maintained as further cases with, overall, a rate ratio controlling for age and sex of 1.60 (95% c.i. 1.15, 2.23), i.e. individuals living in the "North" in 1991 are about one and a half times more likely to have developed vCJD than individuals who were living in the "South" in 1991. The overall rate ratio is slightly less than that estimated last year (1.65), based on 125 cases.

Table 5 **Comparison of cumulative incidence in the "North" of the UK (excluding Northern Ireland) with that in the "South"**

Region	Population aged 10 years and above at the 1991 census	Number (rate/million) of vCJD cases by place of residence at 1st January 1991	
		First 51 cases	Total
"North" (North West, Yorks & Humbs, Northern, Scotland)	16.6 million	26 (1.57)	64 (3.86)
"South" (South West, South East, Wales, West Midlands, East Midlands, East Anglia)	31.2 million	25 (0.80)	76 (2.43)
Total (rate ratio*)	47.8 million	51 (1.94)	140 (1.60)

*North versus South, adjusted for age and sex

Northern cases were slightly older at onset than southern cases (median of 26½ years versus 24½ years; p=0.5), a similar proportion were male (56% versus 54% of southern cases; p=0.8).

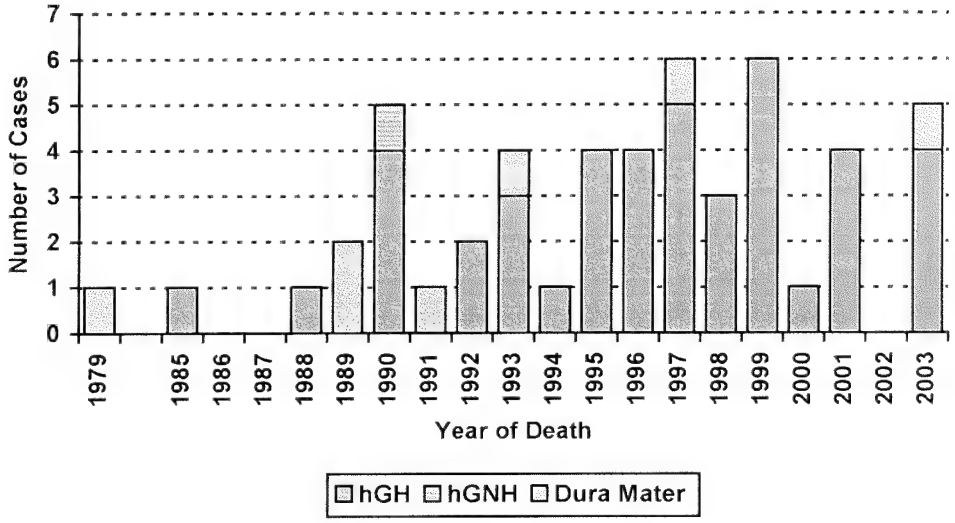
Geographically Associated Cases of variant CJD

Geographically associated cases of variant CJD are defined by two or more cases of probable or definite vCJD with a geographical association, either through proximity of residence or through another link with the same location (occupational, educational or social/recreational). By the end of December 2003 a total of thirteen investigations into geographically associated cases of vCJD had been opened in the UK. Those in eleven localities were concluded and in two were ongoing. The Leicestershire cluster of five cases remains the only statistically significant cluster of cases of vCJD in the UK to date. None of the concluded investigations have revealed any suggestion of possible iatrogenic transmission. No evidence emerged from these investigations in any of the areas apart from Leicestershire of bovine heads being split or brains removed by local butchers in their shops during the relevant time period.

2.3 *Iatrogenic Creutzfeldt-Jakob disease*

Since 1970, up to 31st December 2003, 51 cases of CJD attributable to iatrogenic exposure have been identified, 7 in individuals receiving dura mater implants, 43 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN) (Figure 11).

Figure 11 Deaths from iatrogenic CJD, 1979-2003



The mean age at death of the hGH/hGN group was 30 years (with a range of 20-45 years) and for the dura mater cases 42 years (range 27-59 years).

The first identified iatrogenic case was a dura mater recipient who died in 1979. The first hGH-related death occurred in 1985. Since 1985 in the UK, human pituitary-derived hormones have been replaced by synthetic preparations.

2.4 Transfusion Medicine Epidemiology Review

The Transfusion Medicine Epidemiology Review (TMER) is a collaborative project between the UK NCJDSU and UK Blood Services (UKBS). The main purpose is to investigate whether there is any evidence that CJD or vCJD may have been transmitted via the blood supply.

Methods

vCJD cases (definite and probables) are notified to the UKBS by NCJDSU; a search establishes whether any have acted as donors. Donation records are checked and all components traced through hospital records. Details of all identified recipients are forwarded to NCJDSU for subsequent checking.

In the reverse procedure, patients with vCJD reported to have received blood transfusions are identified by NCJDSU and notified to UKBS. Details of transfusions are traced through hospital records and relevant blood donors identified. The identity of donors is notified to NCJDSU for subsequent checking.

Results

Twenty-seven vCJD cases were reported to have been blood donors, of whom 18 have been traced at blood centres. Components from 15 of these individuals were actually issued to hospitals. It has been established that 49 components were transfused to named recipients (with 3 units discarded and 6 hospitals unable to trace component fate). One of these recipients

was identified as developing symptoms of vCJD 6½ years after receiving a transfusion of red cells donated 3½ years before the donor developed symptoms of vCJD[1].

In the reverse study, 9 vCJD cases were reported to have received blood transfusions. Checks revealed that 2 were not transfused, 2 had transfusions which predated available records and 5 had records of transfusion which could be traced. These 5 individuals had received 122 components of blood (with one patient given 103 components), which have been traced to 120 named donors (including the vCJD donor described above[1]). The donors of two components are not traceable.

Conclusion

These findings raise the possibility of a transfusion transmitted case of vCJD. Infection in the recipient could have been due to past dietary exposure to the BSE agent. However, the age of the patient was well beyond that of most vCJD cases, and the chance of observing a case of vCJD in a recipient in the absence of transfusion transmitted infection is about 1 in 15 000 to 1 in 30 000.[1]

(Collaborators on this project: Dr P.E. Hewitt and Dr C.A. Llewelyn).

2.5 Study of Progressive Intellectual & Neurological Deterioration (PIND)

The aim of this project is to use the mechanism of the British Paediatric Surveillance Unit to identify all cases of progressive intellectual and neurological deterioration in children in the UK, particularly those with features suggestive of vCJD. All cases are discussed by an Expert Neurological Advisory Group of six paediatric neurologists which allocates the cases to a diagnostic category[2].

After almost 7 years surveillance, 1711 patients with suspected PIND have been reported. The Expert Group has discussed 1204 cases, of which 696 have a confirmed underlying cause other than vCJD, being categorised into 112 known neurodegenerative diseases. Among them were six cases of vCJD; four definite and two probable. Three were reported in 1999, one in 2000 and 2 in mid-2001. One girl was aged 12 at onset - the youngest case of vCJD identified to date.

(Collaborators: Dr C. Verity, Dr A. Nicoll, Ms G. Devereux).

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[1] Llewelyn CA, Hewitt PE, Knight RSG, Amar K, Cousens S, Mackenzie J, Will RG. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. Lancet 2004; 363: 417-421.

[2] Verity CM, Nicoll A, Will RG, Devereux G, Stellitano L. Variant Creutzfeldt-Jakob disease in UK children: a national surveillance study. Lancet 2000; 356: 1224-1227.

Section

3

CASE-CONTROL STUDY

Since May 1990 a case-control study of CJD has been carried out in the UK to investigate potential risk factors for variant and sporadic CJD. Patients themselves are usually too unwell to answer questions when they are seen by members of the Unit. Therefore, relatives of patients with suspected CJD are asked to be interviewed using a standard questionnaire, which includes a wide range of questions relating to possible risk factors for CJD, including residential, occupational, dietary and medical histories. To maximise the study's validity, it is important that this interview takes place as early as possible, that is, as soon as a person is suspected as having CJD. We are indebted to the families of those with suspected CJD, who agree to be interviewed at often an extremely difficult time in their lives.

Each type of control group used in a case-control study has advantages and disadvantages in terms of suitability as controls, practicalities of recruitment and cost. Since 1990 there have been variations of control recruitment for the CJD risk factor study:-

1990-1997: For each suspect case, an age- and sex-matched patient at the same hospital was identified as a control.

1998-2002: With the diagnosis of the first cases of variant CJD, it was decided that in addition to hospital controls for variant cases, and instead of hospital controls for sporadic cases, community controls would be recruited, matched for sex and age, through general medical practices (one control for each sporadic case and up to 4 controls for each variant case). Community controls are more suitable than hospital controls for the investigation of potential medical risk factors. However, from the start difficulties were encountered arising from the complex process of recruitment of general practice based controls. Of particular concern was the low response rate to the initial letter from the GP to the potential control. With a low response rate, the results from the study would be hard to interpret because of the potential for selection bias. Therefore, a revised strategy for control recruitment was devised.

2002 to date: Hospital controls continue to be recruited for variant cases. Recruitment of community controls from general practices ceased and was replaced by two new control groups. The first are general population controls, who were recruited using the services of the National Centre for Social Research, which is the largest independent social research institute in Britain. The second new group of controls are friends nominated by relatives of cases. That is, relatives of cases are asked to nominate a friend who would agree to be interviewed about a relative of theirs (the control), who is age- and sex-matched to the case. The degree of relative between control and 'friend' is matched to that between the case and their relative. Consent of the control is sought before the 'friend' is interviewed.

Tables 6 & 7 shows the response rate for controls recruited through general practices and those nominated by relatives of cases. The latter has achieved an overall success rate of control recruitment for variant cases of 50% and for sporadic cases of 55%. Seventy-four hospital controls have been recruited for variant cases. To recruit general population controls the National Centre for Social Research selected 4400 addresses in total; 385 of which were non-residential addresses and considered 'ineligible'. Of the remaining 4015 addresses, 2148 were ineligible because they either did not have an adult of the right age, there was no household member with a living relative or there was no household member resident in the UK between 1980 and 1996. From 1867 eligible addresses, 1065 controls were recruited (57%). 87% (924) of relatives were interviewed, giving a final percentage of 49% for achieved interviews at eligible addresses.

Table 6: General Practice community controls - recruitment process

	Variant CJD Number (%)	**Sporadic CJD** Number (%)
GPs written to asking to participate	116	236
GPs agreeing to participate	90 (78%)	168 (71%)
Controls written to by GP asking for agreement to be contacted by NCJDSU	1758	1219
Controls agreeing to be approached by NCJDSU	329 (19%)	420 (34%)
Controls agreeing to take part	231 (13%)	270 (22%)
Relatives agreeing to take part	203* (12%)	227** (19%)
Relatives interviewed	194	152

* 7 relatives were not required, that is, more than 4 relatives agreed to take part for 7 variant cases.
** 75 relatives were not required, that is, more than one relative to agreed to take part for 75 sporadic cases.

Table 7: Relative nominated controls - recruitment process

	Variant CJD Number	**Sporadic CJD** Number
Relatives of cases approached	20	136
Relatives of cases agreeing to participate	13	84
Friend of relative contacted	9	59
Friend of relative agreeing to participate	8	52
Control contacted	7	52
Control consented	6	50

Data from cases and controls recruited from hospitals, general practices and by the National Centre for Social Research are being analysed currently and will be published when completed. The recruitment of hospital controls for variant cases and relative nominated controls for sporadic and variant cases continues. GP and dental records are being traced for controls that have given consent and potential medical, surgical and dental risk factors will be compared where possible with those of cases.

Section

4

LABORATORY ACTIVITIES

Laboratory investigations are part of the internationally-agreed diagnostic criteria for CJD, both during life (CSF protein analysis and PrP genetic studies) and post-mortem (neuropathology and protein studies). The NCJDSU has facilities to perform all of these investigations, which aid the timely and accurate diagnosis of all forms of CJD and are essential for surveillance purposes.

4.1 Neuropathology – Statement of Progress

The neuropathology laboratory in the NCJDSU continues to maintain a high workload in terms of diagnostic and research activities, including the work of the protein laboratory. The laboratory maintains close links with other neuropathology centres across the UK and overseas with scientific, medical, technical and student visitors over the past year for specialist training purposes. The laboratory has continued its major role in the National Retrospective Review of CJD and Related Disorders and in the retrospective study to detect abnormal PrP in anonymised specimens of appendix and tonsil tissue. The laboratory has developed the PET blot technique for the detection of protease-resistant PrP in paraffin sections; this has been of immense diagnostic value, particularly for cerebral biopsy specimens and cases where there is no frozen tissue available for Western blot analysis. Since 2001 the autopsy rates for sporadic and variant CJD have declined, in keeping with national trends which have been markedly influenced by the outcome of the Alder Hey inquiry. This continues to influence the number of cases examined in 2003, but the figures for both sporadic and variant CJD are increased in relation to comparable figures for 2002. As before, the laboratory continues to act as a source of information to a wide range of professionals involved in health and safety issues relating to CJD. We are most grateful to all neuropathologists, general pathologists and their technical, secretarial and autopsy room staff for their continuing support of the NCJDSU. We are also grateful to the relatives of patients with CJD for allowing us to study this group of devastating disorders.

4.2 Surveillance and workload during 2003

A detailed breakdown of laboratory activities is summarised in Table 8. These demonstrate that the total number of cases referred to the laboratory from the UK has increased in comparison with the previous year, with increases in the numbers of both sporadic and variant CJD cases. Neuropathological referrals are made from pathologists across the UK and overseas. These include cases where a preliminary histological diagnosis of CJD has been made, cases which have undergone autopsy but no histological examination has been undertaken in a patient with suspected CJD, and cases where a

diagnosis of CJD is thought unlikely, but no specific histological diagnosis has been made. The latter are usually referred to help the exclusion of CJD from the differential diagnosis. Material from DH-funded research projects is also referred to the NCJDSU, particularly in the UK Haemophilia Study (Director: Professor Christine Lee, Royal Free Hospital, London). In contrast to last year, the most frequent alternative diagnoses for sporadic CJD is dementia with Lewy bodies, closely followed by Alzheimer's disease. The pathological features of variant CJD cases have been reviewed (see publications list). This has indicated that the pathological phenotype of variant CJD has remained relatively constant over the past 8 years, in terms of the changes occurring in the central nervous system and in peripheral tissues, particularly lymphoid tissues. The neuropathological features of the case of variant CJD associated with blood transfusion were closely similar to other cases of variant CJD investigated in the laboratory.

The laboratory is a major contributor to the World Health Organisation TSE Diagnostics Working Group, and continues to act as an international reference centre for the diagnosis of CJD.

Table 8 Breakdown of Laboratory Activities 1st January 2003 – 31st December 2003

	CURRENT YEAR	PREVIOUS YEAR
REFERRED CASES (UK)		
Sporadic CJD	52	45
Familial CJD	2	1
Variant CJD	10	3
Iatrogenic CJD (growth hormone therapy)	3	0
Gerstmann-Straussler-Scheinker syndrome (GSS)	0	0
Fatal Familial Insomnia	0	0
No evidence of CJD (no alternative diagnosis)*	17	19
Alzheimer's disease	2	4
Dementia with Lewy Bodies	3	4
Other forms of brain disease†	3	6
REFERRED CASES (EUROPEAN UNION)		
Sporadic CJD	5	5
Familial CJD	1	0
Variant CJD	0	0
GSS	0	0
Other forms of brain disease	8	3
REFERRED CASES (REST OF WORLD)		
Sporadic CJD	4	3
Variant CJD	0	2
Other forms of brain disease	6	0
TOTAL NUMBER OF CASES	**116**	**95**

* Cases with no specific histological or biochemical evidence of CJD, in whom no specific alternative diagnosis can be made. These cases are usually submitted for the exclusion of CJD in the differential diagnosis, and the diagnosis given back to the referring pathologist is the diagnosis submitted at the time of referral. Further histological investigations leading to an alternative diagnosis are the responsibility of the referring pathologist.

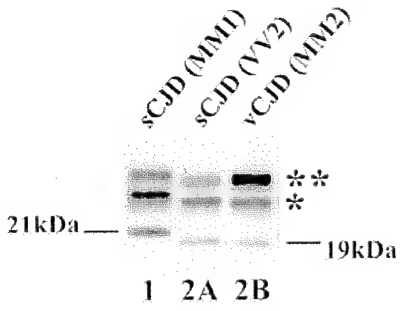
† Other forms of brain disease: malignant glioma (1), metabolic encephalopathy (1), subacute sclerosing panencephalitis (1)

4.3 Protein Laboratory

CNS Tissues

Prion protein isotyping is carried out as a routine diagnostic test on all suspected cases of CJD where fresh brain tissue is received by the NCJDSU. Small quantities of cerebral cortex are homogenized, treated with proteases and the size and abundance of the three PrP^{res} glycoforms determined by Western blot analysis. The prion protein isotype is classified as type 1 if the nonglycosylated form has a molecular weight of ~21kDa or type 2 if the nonglycosylated form has a molecular weight of ~19kDa. The suffix B is used to denote a PrP^{res} isotype where the diglycosylated band predominates. The remaining type 2 cases where the diglycosylated band does not predominate are termed type 2A. The type 2B isotype has previously found to be characteristic of variant CJD (Figure 12).

Figure 12 PrP^{res} Types in Sporadic and Variant CJD



Western blot analysis of protease-resistant prion protein (PrP^{res}) in two cases of sporadic CJD (sCJD) of the MM1 and VV2 subtypes and in a case of variant CJD (vCJD (MM2)). The size of the nonglycosylated (bottom band) is either 21 kDa (termed type 1) or 19 kDa (termed type 2). Diglycosylated PrP^{res} (**) predominates in the variant CJD and the pattern is termed type 2B to distinguish it from type 2 cases in which the monoglycosylated form (*) predominates (type 2A).

A total of 57 UK cases with frozen tissue were received and analysed in 2003, representing a 50% increase in the number of cases referred for analysis in 2001 and 2002. The results of these analyses were as follows (Table 9):

Table 9 Breakdown of UK cases analysed in 2003

Diagnosis	Type	PrP^{res} +ve CNS
CJD (n=48)	Sporadic	38/38
	Variant	8/8[1]
	Iatrogenic	1/1[2]
	Familial (E200K)	1/1[3]
Alternative final diagnosis or not determined (n=9)		0/9

[1] includes one tonsil biopsy
[2]iCJD (MV2A)
[3]fCJD (MM1B)

When the sporadic and variant cases are sub-classified according to the PrP^{res} type and the *PRNP* codon129 genotype, the following results were obtained (Table 10):

Table 10 Isotype/genotype breakdown of UK CJD cases analysed in 2003

Diagnosis	129	Type 1	Type 2A	Type 1 & Type 2[1]	Type 2B	Total
Sporadic CJD	M/M	16	1	1	-	18
	M/V	3	7	3	-	13
	V/V	2	4	1	-	7
	Total	**21**	**12**	**5**	-	**38**
Variant CJD	M/M	-	-	-	8[2]	8
	M/V	-	-	-	-	0
	V/V	-	-	-	-	0
	Total	-	-	-	8	8

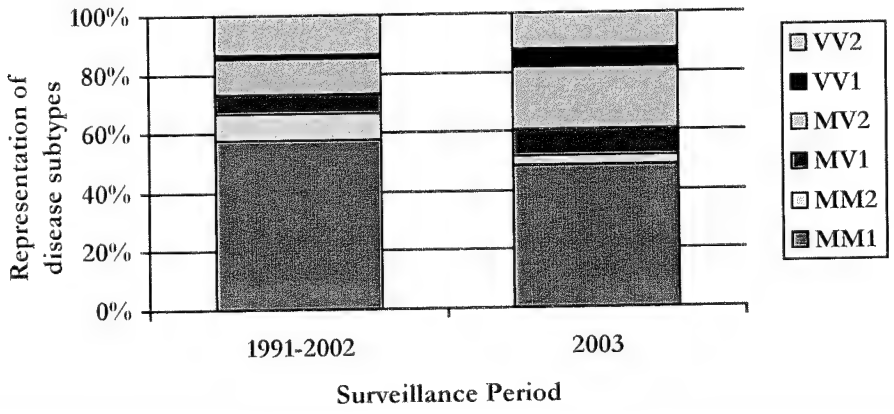
[1]Mixed types are defined as cases where both Type 1 and Type 2 are found in the same sample from one part of the brain or where different types are found in samples from different brain regions.
[2] includes one positive tonsil biopsy.

Four requests for Western blot analysis were also received from non-UK referrals. Three of these were found to have detectable PrP^{res} in CNS specimens, while the fourth was a PrP^{res} negative tonsil biopsy.

Methodological Note: Previously all Western analysis has used the SDS-PAGE and Western transfer method described in Ironside et al (2000) which was itself based on that described in Collinge et al (1996). This year the hand-poured Bio-Rad gel format was replaced with pre-cast NuPAGE 10% Bis-Tris gels (Invitrogen Corporation, Paisley, UK) which were run and transferred according to the manufacturer's instructions. Sample preparation and post-transfer steps remained unaltered.

The results of a long-term study of the PrP^{res} type and *PRNP* codon 129 in the UK sporadic CJD population (Head et al, in press) allow us to compare this year's data with that from the period 1991-2002. The results are broadly similar but show an apparent under-representation of MM1, MM2, VV2 subtypes and an over-representation of MV1, MV2 and VV1 subtypes (Figure 13) which may reflect random variation occurring in these small groupings.

Figure 13 Sporadic CJD subtypes in 2003 and combined preceding years



Peripheral Tissues

The presence of PrP^{res} in peripheral tissues, particularly in the lymphoreticular system, has been thought to be a defining feature of variant CJD. Our Western blot and immunohistochemical studies confirm this and have been published recently in The American Journal of Pathology (Head et al 2004). Two further articles describing the presence and distribution of PrP^{res} in the eye (Head et al 2003a) and in the oral cavity (Head et al 2003b) have also been published. The results are shown in condensed form in Table 11 along with results from a more recent article on the central nervous system (Head et al, Ann Neurol, *in press*).

Table 11 Tissue Distribution of PrP^{res} by Western blotting

System	Organ / tissue	Variant CJD	Sporadic CJD
Nervous system	Brain	+ (59/59)	+ (170/170)
	Trigeminal ganglion	+ (6/7)	+ (2/3)
	Dorsal root ganglion	+ (2/9)	-[1] (0/7)
	Peripheral nerve	- (0/8)	- (0/7)
Lymphoreticular system	Tonsil	+ (7/8)	- (0/7)
	Lymph nodes	+ (7/9)	- (0/7)
	Spleen	+ (8/9)	- (0/6)
	Appendix	-[1] (0/8)	- (0/3)
Eye	Cornea	- (0/2)	- (0/1)
	Iris	- (0/2)	- (0/1)
	Lens	- (0/2)	- (0/1)
	Vitreous body	- (0/2)	- (0/1)
	Choroids and sclera	- (0/2)	- (0/1)
	Neural retina	+ (2/2)	+ (1/1)
	Optic nerve	+ (2/2)	nt
Oral cavity	Dental pulp	- (0/2)	nt
	Gingival	- (0/3)	nt
	Alveolar nerve	- (0/2)	nt
	Salivary gland	- (0/4)	- (0/1)
Other organs and tissues	Heart	- (0/5)	- (0/3)
	Lung	- (0/6)	- (0/3)
	Liver	- (0/7)	- (0/3)
	Kidney	- (0/5)	- (0/3)
	Skeletal muscle	- (0/9)	- (0/7)
	Adrenal gland	- (0/6)	- (0/3)

[1]Tissue PrP^{res} positive by immunohistochemistry
nt = not tested

These observations are unlikely to be definitive since PrP^{Sc} detection methods of increased sensitivity continue to be developed and applied by us and by others. It can therefore be expected that the tissue distribution of PrP^{Sc} (and by inference infectivity) in variant CJD will widen and secondly that lower levels of PrP^{Sc} in peripheral tissues in sporadic CJD may also be found.

4.4 Brain banking activities

The bank of fixed and frozen tissues in the surveillance unit was used extensively in 2003 for diagnostic and collaborative research purposes with colleagues in the UK and overseas. A brain bank manager was appointed in 2002, who has primary responsibility for this unique resource. The activities of the Bank comply with current guidelines from MRC and the Royal College of Pathologists. The Bank and its activities are overseen by the Tissue Management Group established by the Department of Health.

4.5 Molecular Genetics

Familial CJD

Sixty-two cases of familial CJD (excluding cases of GSS) have been identified since 1970 by the NCJDSU (these data are incomplete as formal investigation of familial CJD in the UK is undertaken by the National Prion Clinic in London). Of the 62 cases, 57 were resident in England and 5 were resident in Wales. Twelve cases are still alive. Thirty-three of the cases had insertions in the coding region of the PrP gene, 15 carried the mutation at codon 200 (Glu-Lys), 2 at codon 178 (Asp-Asn, both with methionine at codon 129, ie FFI), one at codon 117 (Ala-Val) and one at codon 210 (Val-Ile). Ten were identified as familial on the basis of relatives known to have had CJD. The mean age at death was 55 years (range 31-77 years).

Codon 129 distribution in sporadic CJD

The distribution of codon 129 genotypes in sporadic CJD has been analysed since the inception of the Unit in 1990. The overall distribution of codon 129 genotypes in sporadic CJD is 66% MM, 17% MV, 17% VV (see Table 12). There appears to be evidence ($p=0.022$) of a change in the codon 129 distribution in sporadic CJD between the periods 1990-1995 and 1996-2003. The explanation for this remains unclear and is being investigated further. It should be noted that not all cases are genotyped (data available on 63%) and, therefore, the codon 129 distribution may reflect selection bias.

Table 12 Codon 129 genotypes of cases of sporadic CJD in the UK, 1990-2003

Deaths from sporadic CJD	**MM(%)**	**MV(%)**	**VV(%)**
Deaths from 1 May 1990 – 31 December 1995	96 (75)	14 (11)	17 (13)
Deaths from 1 January 1996 – 31 December 2003	191 (62)	59 (19)	58 (19)
Total	287 (66)	73 (17)	75 (17)
Genotype distribution for the normal population Pooling data from five studies	(39)	(50)	(11)

Codon 129 distribution in vCJD

All cases for whom genetic data are available (123) were methionine homozygotes at codon 129 of the PrP gene.

The genetic laboratory undertakes genetic analysis on a national and international basis.

4.6 CSF 14-3-3 and other brain specific proteins

The laboratory received 283 CSF samples from January 2003 – December 2003. Of these, 111 were from patients who were referred to NCJDSU as suspect cases of CJD and 152 were from patients who did not have clinical features to merit formal referral as a suspect case of CJD, but in whom the diagnosis remained a possibility. These are termed CSF only referrals. The remaining CSF samples were sent to the laboratory from hospitals outside the United Kingdom. The origin and numbers of these samples are given in Table 13.

Table 13 Number and origin of CSF samples received at the NCJDSU: Jan-Dec 2003

Source	Number of CSF samples (% of total)
CSF from suspect CJD referrals	111 (39%)
CSF only referrals	152 (54%)
Non-UK countries	20 (7%)
Total	283

The number of CSF-only referrals have increased by 55% whilst the number of CSF samples from patients referred to the NCJDSU have increased by 21%. The numbers of CSF samples referred from non-UK countries have halved as Sweden has established a CSF 14-3-3 diagnostic service in Stockholm.

CSF 14-3-3 results in CSF samples received from CJD patient referrals

Of the 111 CSF samples from patients referred to the NCJDSU with suspected CJD, five were blood-stained and unsuitable for 14-3-3 analysis. The CSF 14-3-3 results in the remaining 106 patients are shown in Table 14.

Table 14 CSF 14-3-3 results in patients referred to NCJDSU: Jan– Dec 2003

Type of CJD	Diagnostic group (number of patients)	Positive 14-3-3/ Total number samples tested
Sporadic	Definite	21/23
	Probable	31/31
	Possible	0/1
	Not CJD	15/24
Variant	Probable	6/12
	Not CJD	1/8
Iatrogenic	Definite (hGH)	0/1
	Probable (hGH)	1/1
	Probable (Dura Mater)	0/1
Genetic	Definite E200K mutation	1/1
	Probable E200K mutation	1/2
	Probable GSS (P102L)	1/1
	Not CJD	0/1

Two patients with definite sporadic CJD had a negative CSF 14-3-3. The clinical course in one was atypical and the disease duration was 42 months. The codon 129 genotype was MV and neuropathological examination showed the presence of protease-resistant PrP with a type 2A isoform. The second patient is still alive 13 months after onset.

Three of the 31 patients with probable sporadic CJD are still alive, seven patients have died and are awaiting neuropathological examination and the remaining 21 patients have died without neuropathological confirmation of sporadic CJD. Of the patients who died without neuropathological confirmation of sporadic CJD, four had EEG traces that were considered typical for sporadic CJD whilst 14 had either EEG traces that were not considered typical or EEG traces that were not reviewed by the NCJDSU. Three EEGs are awaiting review. Therefore 14 of the 21 patients with probable sporadic CJD who died without neuropathological confirmation have been classified as probable on the basis of the 14-3-3 result without independent EEG support.

There were 15 patients who were referred as suspect cases of CJD who had a positive 14-3-3 but were not diagnosed with CJD. In seven patients the diagnosis of CJD remains a possibility (one patient has died without undergoing post mortem and 6 cases are still under review). Of the remaining 8 cases, 3 had Alzheimer's disease, 2 patients improved, one patient had vasculitis, one patient had central pontine myelinolysis and one patient had Lewy body dementia.

Of the 12 patients with probable variant CJD (a classification made independent of 14-3-3), six were positive for 14-3-3.

The sensitivity, specificity, positive and negative predictive values for CSF 14-3-3 in the diagnosis of sporadic and variant CJD are given in Table 15.

Table 15 Sensitivity, specificity, positive and negative predictive values for CSF 14-3-3 for the diagnosis of sporadic and variant CJD, based on the 14-3-3 results for definite sporadic and probable variant CJD.

	Sporadic CJD **Positive 14-3-3/ total numbers CSF investigated**	**Variant CJD** **Positive 14-3-3/ total numbers CSF investigated**
Definite CJD	21/23	/
Probable CJD	31/31	6/12
Not CJD	15/24	1/8
Sensitivity	91%	50%
Specificity	38%	88%
Positive Predictive value	57%	86%
Negative Predictive value	88%	54%

CSF 14-3-3 in CSF only referrals

One hundred and fifty-two CSF samples were received as CSF only referrals and constituted 50% of the total number of samples received. As seven CSF samples were blood-stained only 145 were available for analysis. Twenty-three of the 145 CSF samples analysed for CSF 14-3-3 were positive. The diagnoses of these cases are given in Table 16.

Table 16 Diagnoses in patients with positive 14-3-3 results in CSF only referrals

Diagnosis (number of patients)
Central nervous system infection (3)
Improved (3)
Paraneoplastic syndrome (3)
Non-CJD dementia (3)
CNS malignancy (1)
Sydenham's chorea (1)
Cerebral angiopathy (1)
Vascular disease (1)
Unknown (7)

In addition to the above samples, a set of 19 serial CSF samples were received from a patient undergoing pentosan polysulphate treatment.

Summary

The presence of 14-3-3 in the CSF in 14 patients with clinical features of sporadic CJD who died without postmortem and without typical EEG changes, has enabled these patients to be classified as probable sporadic CJD. Without CSF 14-3-3 analysis these patients would have remained as possible cases of sporadic CJD and would not have entered into the annual sporadic CJD figures. As sporadic CJD is a rare disease these 14 cases consititute a significant proportion, approximately 25%, of the annual number of cases.

The number of CSF samples received have increased, with the largest increase being samples received from patients without enough signs or symptoms to be considered a suspect case of CJD. This suggests that CSF 14-3-3 is increasingly being used as a screening test for CJD.

The specificity of 14-3-3 for sporadic CJD has decreased. There are three possibilities for this, one is that this is a chance occurrence, secondly that a change in the analytical and interpretative process has increased the number of false positives detected. There have been no such changes and there is no concomitant increase in the detection of false positives in patients with suspected variant CJD. Thirdly it is possible that the population of patients with suspected sporadic CJD has changed with an increasing number of patients with conditions other than CJD that are associated with positive 14-3-3 being referred to the unit as suspect sporadic CJD cases. This situation will be closely monitored over the next year.

Section

5

NATIONAL CJD CARE TEAM

The national CJD Care Team is based within the National CJD Surveillance Unit and was formed in response to concerns regarding the care of CJD patients. An initial national care coordinator post was established in February 2000 and in September 2001 the National CJD Care Team was formed. Since March 2003 the team has consisted of two co-ordinators and a secretary.

The role of the National CJD Care Team is to provide advice on all forms of CJD to the patients, their family and professional carers, including information on the clinical features, diagnostic procedures and prognosis. The National Care Co-ordinators are available to assist with co-ordination of care locally, by providing the necessary education and support to local health professionals involved in care of CJD patients. They are available to visit patients and their families and will provide advice on specific management issues such as symptom control. The team are supported by neurologists within the unit.

When a referral has been made to the NCJDSU of a likely case of CJD, the co-ordinator makes direct contact with the family and offers the opportunity to meet and to assist with care intervention. Referrals are also made to the Care Team from the National Prion Clinic at St Mary's Hospital and Leah Davidson, who co-ordinates the care of iatrogenic CJD cases. Once contact is made, the co-ordinator can meet with the patient and family on a regular basis, depending on need, to provide support and to assist with co-ordination of local health and social care professions. Post bereavement support is offered to the family after the patient dies or assistance given with accessing more specialised counselling.

The National CJD Care Team is in close liaison with the Department of Health and provides access to the CJD Care Package, which is a sum of money available to assist local authorities with the care of CJD patients. The National CJD Care Team is also responsible for the management of the CJD Advice Network. This is a group of Health and Social Services Professionals who have had experience of working with CJD and are available to share their experience and provide advice with other professionals. Audit is performed on contacts made to the Network and members will be kept up to date with recent developments within CJD with a six monthly newsletter.

From the establishment of the first National Care Co-ordinator post until 31st December 2003, the co-ordinators have been in contact with, and/or provided access to care funds, to 67 variant cases, 62 sporadic cases, 14 familial cases and 6 iatrogenic cases. The care team is currently involved with 8 variant cases, 9 sporadic cases and 9 familial cases. The number of variant cases has remained constant over the last 2 years, however increased referrals of sporadic, familial and iatrogenic patients have led to an increased workload for the care team and to increased expenditure from the CJD Care Fund.

The National Care Coordinators undertook 267 patient visits and case conferences during 2003 compared to 194 in 2002. (Tables 17 and 18). In addition, 35 teaching sessions were provided to professionals involved in the provision of care to CJD patients. A further 17 talks/teaching sessions were provided to various organisations/conferences.

Table 17 Patients alive and visited per month in 2003

Month	Alive	Visited
January	28	10
February	29	11
March	31	10
April	30	10
May	34	14
June	29	14
July	30	10
August	31	7
September	26	12
October	25	12
November	25	13
December	27	5

Table 18 Case Conferences and Family Visits by Co-Ordinators January to December 2003

Subtype of CJD	Number
Variant	157
Sporadic	78
Familial/Genetic	25
Iatrogenic	7
Total	267

Expenditure from the National CJD Care Fund has increased and to the end of December 2003 a total of £630,653 has been spent, comprising £322,575 in 2003 compared with £243,476 in 2002 and £64,602 in 2001. A breakdown of expenditure during 2003 is shown in Table 19.

There is a difference in expenditure between the different disease subtypes which reflects the variability of their progression. With familial/genetic CJD cases generally having a much longer duration, this enables local services to plan ahead for the patients' changing needs. However, in relation to sporadic CJD cases, by the time the co-ordinators are referred patients with this disease subtype, they are usually in the advanced stages of the condition and will have a much shorter prognosis.

Table 19 Care Fund Payments - January to December 2003

Description	Amount
Accommodation	1,046.23
Adaptations	23,057.56
Alternative Therapy	11,143.45
Care Hire	35,432.91
Childcare	2,970.50
Counselling	1,000.00
Equipment	50,830.87
Nursing	186,264.22
Physiotherapy	910.00
Respite	5,828.60
Social Care	1,913.79
Transport	2,177.00
TOTAL	**£322,575.13**

Section

6

PUBLICATIONS IN 2003

1. Andrews NJ, Farrington CP, Ward HJT, Cousens SN, Smith PG, Molesworth AM, Knight RSG, Ironside JW, Will RG. Deaths from variant Creutzfeldt-Jakob disease in the UK. Lancet 2003;361:751-752.

2. Armstrong RA, Cairns NJ, Ironside JW, Lantos PL. Does the neuropathology of human patients with variant Creutzfeldt-Jakob disease reflect haematogenous spread of the disease? Neurosci lett2003; 348: 37-40.

3. Armstrong RA, Lantos PL, Ironside JW, Cairns NJ. Differences in the density and spatial distribution of florid and diffuse plaques in variant Creutzfeldt-Jakob disease (vCJD). Clin Neuropathol 2003; 22: 209-214.

4. Armstrong RA, Lantos PL, Ironside JW, Cairns NJ. Spatial correlation between the vacuolation, prion protein deposition and surviving neurones in patients with variant Creutzfeldt-Jakob disease (vCJD). J Neural Transm 2003; 110: 1303-1311.

5. Barr J, Harris N, Chapman K, Head MW, Fraser J. A proteomics (SELDI) approach to disease markers for TSEs. International Conference on Transmissible Spongiform Encephalopathies Book of Abstracts, 49. 2003.

6. Barron R, Jamieson E, Thomson V, Melton D, Will R, Ironside JW, Manson J. The 101 L mutation in murine PrP can alter transmission across three species barriers. In: Fraser JR (ed): Recent Progress in Transmissible Spongiform Encephalopathies. Neuropathol and Appl Neurobiol 2003; 29(5): 208. (abstract)

7. Bird SM, Will RG. Dedication, yet uncertainty. Statistical Methods in Medical Research 2003;12:175-176.

8. Bishop MT, Will RG, Aitchson L, Baybutt H, Gall E, Hart P, Tuzi N, Manson JC. Novel gene targeted transgenic mice as models for codon 129 disease association in Creutzfeldt-Jakob disease. Munich Conference, 2003 (abstract).

9. Boelle P-Y, Thomas G, Valleron A-J, Cesbron J-Y, Will R. Modelling the epidemic of variant Creutzfeldt-Jakob disease in the UK based on age characteristics: updated, detailed analysis. Statistical Methods in Medical Research 2003;12:221-233.

10. Brandel J-P, Preece M, Brown P, Croes E, Laplanche J-L, Agid Y, Will R, Alperovitch A. Distribution of codon 129 genotype in human growth hormone-treated CJD patients in France and the UK. Lancet 2003;362:128-130.

11. Brown P, Bradley R, Detwiler L, Dormont D, Hunter N, Wells GAH, Wilesmith J, Will R, Williams E. Transmissible spongiform encephalopathy as a zoonotic disease. Brussels, 2003.

12. Budka H, Head MW, Ironside JW, Gambetti P, Parchi P, Zeidler M, Tagliavini F. Sporadic Creutzfeldt-Jakob disease. In: Dickson DW (ed). Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders. Basel, ISN Neuropath Press; 2003, pp287-297.

13. Collie DA, Summers DM, Sellar RJ, Ironside JW, Cooper S, Zeidler M, Knight R, Will RG. Diagnosing variant Creutzfeldt-Jakob disease with the pulvinar sign: MR imaging findings in 86 neuropathologically confirmed cases. Am J Neuroradiol 2003;24:1560-1569.

14. Cousens S, Everington D, Ward HJT, Huillard J, Will RG, Smith PG. The geographical distribution of variant Creutzfeldt-Jakob disease in the UK: what can we learn from it? Statistical Methods in Medical Research 2003;12:235-246.

15. Cousens SN, Ward HJT, Everington D, Will RG, Smith PG. The geographical distribution of vCJD in Great Britain. In: Fraser JR (ed): Recent Progress in Transmissible Spongiform Encephalopathies. Neuropathol and Appl Neurobiol 2003; 29(5): 208. (abstract)

16. Everington D, Ward HJT, Cousens SN, Will RG. Population density and variant Creutzfeldt-Jakob disease (CJD). International Conference on Transmissible Spongiform Encephalopathies Book of Abstracts, 61. 2003.

17. Fagge TF, Barclay GR. Analysis of PrP expression in blood of CJD patients by DELFIA and flow cytometry. Munich Conference, 2003 (abstract).

18. Fraser E, McDonagh AM, Head M, Bishop M, Ironside JW, Mann DM. Neuronal and astrocytic responses involving the serotonergic system in human spongiform encephalopathies. Neuropathol and Appl Neurobiol 2003; 29(5): 482-295.

19. Green AJE, Knight RSG, Ironside JW. Cerebrospinal fluid Tau protein as a diagnostic test for variant Creutzeldt-Jakob disease. International Conference on Transmissible Spongiform Encephalopathies Book of Abstracts, 45. 2003.

20. Green AJE, Sivtseva TM, Al'bina PD, Osakovsky VL, Vladimirtsev VA, Zeidler M, Knight RS, Plaonov FA, Shatunov A, Alekseev VP, Krivosshapkin VG, Masters CL, Gajdusek DC, Goldfarb LG. Viliuisk encephalomyelitis: intrathecal synthesis of oligoclonal IgG. J Neuro Sciences 2003;212:69-73.

21. Head MW, Ritchie D, McLoughlin V, Ironside JW. Investigation of PrP^{res} in dental tissues in vaiant CJD. Br Dent J 2003; 195(6): 339-343.

22. Head MW, Bunn TJR, Bishop M, Knight R, Will R, Ironside JW. Heterogeneity in the abnormal prion protein isoforms in the brains of sporadic but not variant Creutzfeldt-Jakob disease patients. Conference . 2003.

23. Head MW, Northcott V, Rennison K, Ritchie D, McCardle L, Bunn TJR, McLennan NF, Ironside JW, Tullo AB, Bonshek RE. Prion protein accumulation in eyes of

patients with sporadic and variant Creutzfeldt-Jakob disease. Investigative Ophthalmology & Visual Science 2003; 44(1): 342-346.

24. Hill AF, Joiner S, Wadsworth JDF, Sidle KCL, Bell JE, Budka H, Ironside JW, Collinge J. Molecular classification of sporadic Creutzfeldt-Jakob disease. Brain 2003;126:1333-1346.

25. Hilton DA, Ironside JW. Screening for variant Creutzfeldt-Jakob disease. JNNP 2003;74(6):828-829.

26. Ironside JW. The spectrum of safety : variant Creutzfeldt-Jakob disease in the United Kingdom. Semin Hematol 2003; 40 (Suppl 3): 16-22.

27. Ironside JW. Variant Creutzfeldt-Jakob disease. Vet Res Comm 2003; 27 (Suppl 1): 11-13.

28. Ironside JW, Head MW, Will RG. Variant Creutzfeldt-Jakob disease; In: Dickson DW (ed): Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders. Basel, ISN Neuropath Press pp 310-317.

29. Ironside JW, Head MW. Variant Creutzfeldt-Jakob disease and its transmission by blood. J Thromb Haemost 2003; 1: 1479-1486.

30. Ironside JW. What is to be gained from the study of human transmissible spongiform encephalopathies? In: Fraser JR (ed): Recent Progress in Transmissible Spongiform Encephalopathies. Neuropathol and Appl Neurobiol 2003; 29(5): 207 (abstract)

31. Kapur N, Abbott P, Lowman A, Will RG. The neuropsychological profile associated with variant Creutzfeldt-Jakob disease. Brain 2003; 126(12): 2693-2702.

32. Knight R. Variant CJD: the present position and future possibilities. Int J Pediatric Otorhinolaryngology 2003;67S1:S81-S84.

33. Knight R, Will B. Prion Diseases; in: Caplan LR, Dichgans J, Diener HC, Kennard C (eds). Neurological Disorders: Course and Treatment. USA, Academic Press pp 707-720.

34. Korth C, Kaneko K, Groth D, Heye N, Telling G, Mastrianni J, Parchi P, Gambetti P, Will R, Ironside J, Tremblay P, DeArmond SJ, Prusiner SB. Abbreviated incubation times for human prions in mice expressing a chimeric mouse-human prion protein transgene. PNAS 2003;100 (8):4784-4789.

35. Kovacs GG, Koperek O, Ritchie D, Ironside JW, Wick G, Budka H. Do mobile cells contribute to prion transport? In: Fraser JR (ed): Recent Progress in Transmissible Spongiform Encephalopathies. Neuropathol and Appl Neurobiol 2003; 29(5): 207. (abstract)

36. Lim R, Dhillon B, Kurian KM, Aspinall PA, Fernie K, Ironside JW. Retention of corneal epithelial cells following Goldmann tonometry: implications for CJD risk. Br J Ophthalmol 2003;87:583-586.

37. Manson J, Barron RM, Baybutt H, Tuzi NL, Jamieson E, Gall E, Aitchison L, Thomson V, McConnell I, Moore R, Melton DW, Ironside J, Will R. Targeting the

PrP gene. International Conference on Transmissible Spongiform Encephalopathies Book of Abstracts, 52. 2003.

38. McCormack J, Baybutt H, Everington D, Will R, Ironside J, Manson J. Polymorphism in the regulatory regions of the PRNP gene associated with susceptibility to CJD. International Conference on Transmissible Spongiform Encephalopathies Book of Abstracts, 51. 2003.

39. Molesworth AM, Gill ON, Ward H, Everington D, Cousens S. Investigating geographically associated cases of variant Creutzfeldt-Jakob disease in the United Kingdom. Health Protection Agency Inaugral Conference, Warwick, September 2003.

40. Nurmi MH, Bishop M, Strain L, Brett F, McGuigan C, Hutchinson M, Farrell M, Tilvis R, Erkkila S, Simell O, Knight R, Haltia M. The normal population distribution of PRNP codon 129 polymorphism. Acta Neurol Scand 2003; 108: 374-378.

41. Lowman A, Everington D, Ward H, Will RG. Medical and surgical interventions in the first 100 cases of variant Creutzfeldt-Jakob disease in the UK - a risk factor for the development of the disease. Association of British Neurologists, 2003.

42. Paramithiotis E, Pinard M, Lawton T, LaBoissiere S, Leathers VL, Wen-Quan Z, Estey LA, Lamontgne J, Lehto MT, Kondejewski LJ, Francoeur GP, Papadopoulous M, Haghighat A, Spatz SJ, Head M, Will R, Ironside J, O'Rourke K, Tonelli Q, Ledebur HC, Chakrabartty A, Cashman NR. A prion protein epitope selective for the pathologically misfolded conformation. Nature Medicine 2003.

43. Pepys MB, Bybee A, Booth DR, Bishop MT, Will RG, Little AM, Prokupek B, Madrigal JA. MHC typing in variant Creutzfeldt-Jakob disease. Lancet 2003;361:487-489.

44. Petzold A, Jenkins R, Watt HC, Green AJE, Thompson EJ, Keir G, Fox NC, Rossor MN. Cerebrospinal fluid S100B correlates with brain atrophy in Alzheimer's disease. Neurosci Lett 2003; 336: 167-170.

45. Petzold A, Keir G, Green AJE, Giovanonni G, Thompson EJ. A specific ELISA for measuring neurofilament heavy chain phosphoforms. J Immunol Methods 2003; 278(102): 179-190.

46. Richard M, Biacabe A-G, Streichenberger N, Ironside JW, Mohr M, Kopp N, Perret-Liaudet A. Immunohistochemical localization of 14.3.3 zeta protein in amyloid plaques in human spongiform encephalopathies. Acta Neuropathol (Berl) 2003; 105(3): 296-302.

47. Ritchie D, Ironside J. Advances in the immunodetection of prion protein in peripheral tissues of variant CJD. International Conference on Transmissible Spongiform Encephalopathies Book of Abstracts, 45. 2003.

48. Satoh K, Muramoto T. Tanaka T, Kitamoto N, Ironside JW, Nagashima K, Yamada M, Sato T, Mohri S, Kitamoto T. Association of an 11-12 kDa protease-resistant prion protein fragment with subtypes of dura graft-associated Creutzfeldt-Jakob disease and other prion diseases. J Gen Virol 2003; 84: 2885-2993.

49. Smith AJ, Bagg J, Ironside JW, Will RG, Scully C. Prions and oral cavity. J Dent Res 2003;82(10):769-775.

50. Taguchi Y, Mohri S, Ironside JW, Muramoto T, Kitamoto T. Humanized knock-in mice expressing chimeric prion protein showed varied susceptibility to different human prions. Am J Pathol 2003; 163: 2585-2593.

51. Ward H, Cousens S, Everington D, Lowman A, Smith-Bathgate B, Leitch M, Cooper S, Knight R, Smith P, Will R. Vaccines and Creutzfeldt-Jakob disease (CJD). International Conference on Transmissible Spongiform Encephalopathies Book of Abstracts, 57. 2003.

52. Ward HJ, Head MW, Will RG, Ironside JW. Variant Creutzfeldt-Jakob disease. Clin Lab Med 2003;23(1):87-108.

53. Ward HJT, Everington D, Sanchez-Juan P, Smith A, Cooper S, Heath C, Knight RSG, Will RG. Secondary transmission of variant Creutzfeldt-Jakob disease? International Prion Conference, Munich 2003.

54. Weller B, Knight R, Will R. An overview of the care issues for Creutzfeldt-Jakob disease. European J Palliative Care 2003;10(1):5-8.

55. Will RG. Human prion diseases; in: Warrell DA, Cox TM, Firth JD, Benz EJJ (eds): Oxford Textbook of Medicine. Oxford, Oxford University Press pp 1046-1053.

56. Will RG. The biology and epidemiology of variant Creutzfeldt-Jakob disease. Bulletin et Memoires de l'Academie Royale de Medicine de Belgique 2003;158:250-257.

57. Will RG. Variant Creutzfeldt-Jakob disease and bovine spongiform encephalopathy: current status; in: Ragaini R (ed): International Seminar on Nuclear War and Planetary Emergencies - 27th Session - 2002. Singapore, World Scientific Publishing Co Pte Ltd pp 668-673.

58. Will RG, Knight RSG, Spencer MD. Neuropsychiatric aspects of variant Creutzfeldt-Jakob disease.; in: Ragaini R (ed): International Seminar on Nuclear War and Planetary Emergencies - 27th Session - 2002. Singapore, World Scientific Publishing Co. Pte. Ltd. pp 674-682.

59. Will RG. Progress with Prions. Transfusion Medicine 2003; 13(1): 2. (abstract)

60. Will RG. Variant CJD - what are the risks? In: Fraser JR (ed): Recent Progress in Transmissible Spongiform Encephalopathies. Neuropathol and Appl Neurobiol 2003; 29(5): 208. (abstract).

61. Will RG. Acquired prion disease: iatrogenic CJD, variant CJD, kuru. Br Med Bull 2003; 66: 255-265.

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